

REMARKS

In view of the following Remarks, the Examiner is requested to withdraw the rejection and allow Claims 27-34 and 45-47, the only claims pending and currently under examination in this application.

FORMAL MATTERS:

Claim 27 is amended. As this amendment is provided solely to put the claims in form for allowance or appeal and raises no new issues, the Examiner is requested to enter this amendment.

No new matter is added. As such, the Examiner is requested to enter the above amendments.

STATUS OF THE CLAIMS

The Examiner has indicated that Claims 45-47 are withdrawn as being drawn to methods of transfecting a population of cells, and as such, are distinct from the originally presented and prosecuted method claims of making a non-cellular nucleic acid library (p. 2, l. 3-9). Applicants respectfully submit that Claims 45-47 are, in fact, further descriptions of the non-cellular nucleic acid library that is made by the method of making a non-cellular nucleic acid library discussed in Claim 27 and that, as such, they should not be withdrawn. The Examiner indicated in the Interview dated July 8, 2010 (see summary below) that, should this be the case, Applicants should treat these claims as a species election and indicate which group they would like to have searched first. Applicants herein elect "anti-sense library", Claim 46.

INTERVIEW SUMMARY

Applicants thank Examiner Wessendorf for the courtesy of conducting a telephone interview on July 8, 2010 with Applicant's representatives Bret Field and Elizabeth Alcamo.

During the interview, the status of Claims 45-47 (newly presented in the response filed March 24, 2010 and considered Withdrawn by the Examiner in the Final Office Action) was discussed. The Examiner suggested treating these claims as a species election and indicating in the next Response which species the Applicant would like to have searched first. The Applicants have done so above.

In addition, the Rejection under 35 U.S.C. §112, 2nd paragraph for the alleged indefiniteness of the element "two or more" in Claim 27 was discussed. Applicants'

representatives suggested removing the phrase, which the Examiner indicated **would be** sufficient in overcoming the rejection.

Also discussed was the Rejection under 35 U.S.C. § 112, 1st paragraph for an alleged lack of written description for the claimed genus of nucleic acids that could be used as a starting material in the claimed method. The Examiner indicated that a demonstration of knowledge in the art that the pending claimed method could be used to make non-cellular nucleic acid libraries from nucleic acid material other than ESTs may be considered persuasive in overcoming the rejection. Applicants have provided such a demonstration below.

Also discussed were the Rejections under 35 U.S.C. § 102 and the significance of the claim limitations "amplifying each of said pooled collection to produce amplified pooled collections" and "wherein said non-cellular nucleic acid library is a collection of separate nucleic acids with a sequence representation profile that is substantially the same as the initial sequence representation profile" to the claims and in overcoming art rejections of the record. At the conclusion of this interview, the Examiner agreed that the claims patentably distinguished over the cited reference by Chengtao and that this rejection would be withdrawn upon filing of this response.

It is believed that the above summary provides a true and accurate account of the telephonic interview.

REJECTIONS UNDER §101

Claims 27-34 are rejected under 35 U.S.C. 101 because the claimed invention allegedly lacks patentable utility. The Examiner asserts that "[t]he claimed method of making a non-cellular library from a set of known collections of nucleic acids e.g., EST (expressed sequence tags) produces an intermediate product (library), which do not have a specific, disclosed utility." (page 4, lines 16-19)

Claim 27, from which the remaining pending claims depend, recites a method of producing a non-cellular nucleic acid library, the method comprising: "(a) dividing an initial set of a plurality of separate nucleic acids into at least two pooled collections of nucleic acids having an initial sequence representation profile, wherein each pooled collection includes not more than about 100 distinct nucleic acids; (b) amplifying each of said pooled collections to produce amplified pooled collections; and (c) combining said amplified pooled collections to produce said non-cellular nucleic acid library, wherein said non-cellular nucleic acid library has a sequence representation profile that is substantially the same as said initial sequence representation

profile.” Thus, what is claimed is a method of making non-cellular nucleic acid libraries, where the sequence representation profile of the library that is made is substantially the same as the initial sequence representation profile.

Applicants respectfully submit that methods of making nucleic acid libraries have a clear, specific and substantial utility in the art. For example, methods of making nucleic acid libraries are useful to artisans at biotechnology companies such as Invitrogen and Clontech, which sell nucleic acid libraries to practitioners. Furthermore, to artisans at such companies, methods of making nucleic acid libraries that “have a sequence representation profile that is substantially the same as the initial sequence representational profile” would be of particularly great utility, because such libraries are of greater commercial value: they provide better coverage of the genome than do libraries in which certain nucleic acid species have a higher representation than other nucleic acid species, and as such, are more desirable to practitioners. Likewise, methods of making nucleic acid libraries that “have a sequence representation profile that is substantially the same as the initial sequence representational profile” would also be of great utility to artisans that make libraries for their own studies, for this same reason: greater coverage, and hence, greater efficiency. Thus, methods of making non-cellular nucleic acid libraries, where the sequence representation profile of the library that is made is substantially the same as the initial sequence representation profile, have a clear, specific, and substantial utility.

In making this rejection, the Examiner asserts on page 5, lines 5-13, that:

The method has no patentable utility since it simply collects data from a known collection of data and dividing it into smaller portions to obtain the initial compound from which the (fragment) sets are derived/obtained. It is not apparent from the specification Examples of any specific utility for the claim method. Even assuming that a library is obtained still the library, an intermediate product, has to undergo screening in the hope that the obtained product has a patentable utility.

Moreover, the Examiner asserts on page 6, lines 3-10, that:

The claimed DNA library of plasmids can be used only to gain further information about the underlying genes. The claimed DNA library themselves are not an end of [applicant's] research effort, but only tools to be used along the way in the search for a practical utility. Applicants do not identify the function for the underlying DNA library of non-cellular nucleic acids.

Applicants submit that the specification teaches that a nucleic acid library is “a collection of nucleic acids, where each constituent nucleic acid member of the library is of known

sequence and corresponds to a known chromosomal transcript" (p. 6, l. 30-32) Hence, and contrary to the Examiner's assertions, the pending claimed methods are not for "simply collect[ing] data from a known collection of data and dividing it into smaller portions to obtain the initial compound from which the fragment sets are derived/obtained," but rather for the production of a composition of matter, i.e. a collection of nucleic acids, where each constituent nucleic acid member of the library is of known sequence and corresponds to a known chromosomal transcript, wherein the collection has a sequence representation profile that is substantially the same as said initial sequence representation profile.

Furthermore, and contrary to the Examiner's assertions, nucleic acid libraries do have a patentable utility in and of themselves, namely as tools that enable researchers to analyze the roles of nucleic acids represented therein in modulating various biological processes, e.g., cellular growth, sensitivity to infectious agents or chemical substances, the ability of a cell to differentiate, cell morphology, cellular response to changes in the environment, etc. This utility is asserted in the subject patent specification, page 20, line 30 - page 22, line 32, and an exemplary use for one such nucleic acid library produced by the pending claimed method is set forth in great detail on page 32, line 24 – page 41, line 27. In this working example, Applicants identified a problem to be solved, namely identifying the mechanistic basis of cellular sensitivity to anthrax, and then used a nucleic acid library produced by the claimed method for its investigation. Accordingly, the product of the claimed method is a research tool which finds use in, for example, screening assays to analyze nucleic acids for their roles as candidate agents in modulating biological processes.

With regard to research tools, in particular research tools in the context of screening assays, the MPEP is very instructive. Specifically at MPEP § 2107.01, Part I, the MPEP states:

Research Tools

Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact “useful” in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as “research tool,” “intermediate” or “for research purposes” are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

Thus, the MPEP dictates that “screening assays, and nucleotide sequence techniques have a clear, specific and unquestionable utility”. Applicants respectfully submit that if screening assays themselves have utility, so, too must libraries used in those screening assays and methods for making such libraries. Furthermore, since the instant claims are directed to methods of making tools useful in screening assays, the subject matter of the instant claims, i.e. methods of making the libraries used in these assays, must, too, have a clear, specific and unquestionable utility.

Further, the Federal Circuit has emphasized the importance to biotechnology of patenting research tools. In *Integra Lifesciences I, Ltd. v. Merck KGaA* (Fed. Cir. 2003) 02-1052, 02-1065, it was stated that “patented tools often facilitate general research to identify candidate drugs, as well as downstream safety-related experiments on those new drugs.” (emphasis added)

Even Judge Newman’s dissent in *Integra Lifesciences I, Ltd. v. Merck KGaA* maintained the importance of patenting research tools, stating that “A research tool is a product or method whose purpose is use in the conduct of research, whether the tool is an analytical balance, an assay kit, a laser device (as in *Madey v. Duke University*), or a biochemical method such as the PCR (polymerase chain reaction). It is as subject to the patent right as is any other device or

method, whether it is used to conduct research or for any other purpose. Use of an existing tool in one's research is quite different from study of the tool itself." (emphasis added) Thus, Judge Newman provides a distinction between a product for use in research and a product that can only be the subject of research. Applicants respectfully submit that the nucleic acid libraries produced by the pending claimed method are a research tool and not themselves the subject of investigation. Accordingly, the prevailing case law such as that of *Integra Lifesciences I, Ltd. v. Merck KGaA* supports the Applicant's position that the nucleic acid libraries produced by the pending claimed methods, and hence the pending claimed methods themselves, have a specific, substantial, and credible utility.

Consistent with these arguments, the USPTO has issued a number of patents in the last year alone for methods of making and/or using nucleic acid libraries (see, e.g. US 7,655,791 (February 2, 2010); US 7,635,666 (December 22, 2009); US 7,629,170 (December 8, 2009); US 7,582,446 (September 1, 2009); US 7,576,258 (August 18, 2009); US 7,547,662 (June 16, 2009); US 7,504,216 (March 17, 2009); US 7,488,583 (February 10, 2009)), as well as for nucleic acid libraries themselves (see, e.g., US 7,585,957 (September 8, 2009); US 7,491,531 (February 17, 2009); and US 7,582,446 (September 1, 2009)). Likewise, the Examiner of the instant application, Examiner Wessendorf, has allowed a number of patents drawn to methods of making and/or using nucleic acid libraries (see, e.g. 7,488,590 (February 10, 2009); 7,432,063 (October 7, 2008); 7,416,847 (August 26, 2008); 7,390,619 (June 24, 2008); 7,270,969 (September 18, 2007); 7,122,330 (October 17, 2006); 6,994,982 (February 7, 2006); and 6,897,028 (May 24, 2005). Accordingly, it would not be inconsistent with current USPTO practice to find that the products of the claimed methods, namely, nucleic acid libraries, do in fact have a specific, substantial and credible utility and that, as such, the methods of the pending claims for preparing this products meet the criteria for utility under 35 U.S.C. §101.

Finally, Applicants wish to emphasize that, as discussed above, what is claimed is a method of making nucleic acid libraries, not any one particular nucleic acid library itself. As discussed above, nucleic acid libraries could, in fact, be the end of an artisan's efforts, if, for example, the artisan worked for a biotechnology company that sold nucleic acid libraries to other scientists. To such an artisan, methods of making nucleic acid libraries that "have a sequence representation profile that is substantially the same as said initial sequence representational profile," as is characteristic of nucleic acid libraries made by the pending claimed method would be of great utility.

Thus, Applicants maintain that the specification in view of the art provides a specific, substantial and credible utility for the nucleic acid library made by the pending claimed method and, consequently, for the pending claimed method itself.

In response, the Examiner asserts on page 9, line 13 through page 10, line 7, that:

[A]s acknowledged by applicants above, the nucleic acid library is used to investigate the mechanistic bases of cellular sensitivity to anthrax. Furthermore, the instant claim is not to a method of screening [but] rather to a method of making an intermediate compound i.e., a nucleic acid collection or library. The research tools cited by applicants such as screening assays have a clear, specific and unquestionable utility. Inventions that have a specifically identified utility must be distinguished from those whose utility which requires further research to identify or reasonably confirm. Research tools (such as screening assays and etc.) are useful in the sense that they can be used in conjunction with other method steps to evaluate materials other than themselves or to arrive at some result. The claimed combinatorial libraries are not research tools in this sense. Rather, they are themselves the subject of basic research, whose usefulness or lack thereof has yet to be established. (emphasis added)

Additionally, the Examiner asserts on page 11, line 15 through page 12, line 5, that:

[E]ach case is treated on its own merits. Notably, the patents issued by the present examiner are mostly drawn to screening [a] specific library. The claims of the issued patent are unlike the instant method of making [an] EST library. The instant EST sequence forms only a part of a whole nucleic acid sequence. It is not apparent whether applicants are claiming the whole sequence of the EST or EST gene as part of a nucleic acid sequence. The single species obtained from a consortium does not disclose whether EST as a gene of a nucleic acid or the whole nucleic acid sequence itself. Hence, it is not apparent from the instant EST library whether in fact this is where the utility of the whole (unsequenced or sequenced) nucleic acid resides. (emphasis added)

Applicants respectfully submit that if, as the Examiner asserts, "screening assays have a clear, specific and unquestionable utility", how can it be that a tool used in a screening assay does not, or that a method of making that tool does not? How could that screening assay be performed without that tool? And how could the tool used in that screening assay be made without a method? If the screening assay has a clear, specific and unquestionable utility, so, too, must the tools used in that screening assay, and so, too, must the methods of making those tools.

Furthermore, with regard to the Examiner's assertion that screening libraries "are not research tools" and that "Rather, they are themselves the subject of basic research", Applicants

respectfully submit that the subject of the basic research is *not* the research library, but rather the cellular process under study. Scientists do not embark upon screening methods to find out what is in the library they are using. Rather, they embark upon screening methods to find out what is going on inside the cell, e.g. to determine the proteins involved in cellular processes, e.g. to identify targets to modulate to modulate those cellular processes.

Finally, with regard to the Examiner's assertions that "it is not apparent whether applicants are claiming the whole sequence of the EST or EST gene as part of a nucleic acid sequence", Applicants respectfully submit that, as discussed further below in response to the rejection under 35 U.S.C. §112, this information is irrelevant. What is claimed is a method of making a nucleic acid library, which one of ordinary skill in the art would recognize could be used with nucleic acids from any source.

Thus, Applicants maintain that methods of making screening libraries have a very specific, substantial and credible utility. Reconsideration and withdrawal of the rejection is respectfully request.

REJECTIONS UNDER §112, ¶1

Claims 27-34 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

In making this rejection, the Examiner asserts on page 13, line 19 – page 14, line 7 that:

The specification fails to describe the genus claim method of producing any kind or type of generic non-cellular nucleic acid library of such enormous scope. A claim to such enormous scope should have a corresponding written description that would lead one skilled to the said enormous genus claim. However, the specification at e.g., page 11, lines 10-13 merely provides definitions for each of the claim term. The detail description at e.g., page 33 is drawn to an EST library obtained from human genes from IMAGE consortium. The specification also does not describe this consortium from which the EST human genes are obtained.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 U.S.P.Q.2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991).

As discussed in the previous response, the Examiner appears to be focused on the scope of what is able to be made by the pending claimed method, i.e. "any kind" of non-cellular nucleic acid library. Applicants respectfully maintain that, in view of the teachings in the specification and the level of skill in the art, such a scope is not unduly broad.

For example, the specification teaches at page 9, lines 1-8, that non-cellular nucleic acid libraries produced by methods of the pending claims are made from an initial set of separate nucleic acids, generally DNA. The specification teaches at page 9, lines 20-24, that the initial set of separate nucleic acids is an initial set of distinct nucleic acids of differing sequence, where any two given nucleic acid members in a given set are considered distinct or different if they comprise a stretch of at least 50, usually at least 100, nucleotides in length in which the sequence similarity is less than 95% or lower. The specification teaches at page 16, lines 30-32, that in many embodiments, the initial set of separate nucleic acids used to produce the subject libraries is a set of expressed sequence tags (ESTs). The specification provides a working example in which the initial set of separate nucleic acids is a collection of human ESTs obtained from the IMAGE consortium.

Applicants submit that although the specification only provides a working example using a human EST collection, there is no reason to believe that other sets of separate nucleic acids could not similarly be divided into at least two pooled collections of nucleic acids having an initial sequence representation profile, wherein each pooled collection includes not more than about 100 distinct nucleic acids; that those pooled collections could not be similarly amplified to produce amplified pooled collections; and that those amplified pooled collections could not be similarly combined to produce a non-cellular nucleic acid library, wherein the non-cellular nucleic acid library has a sequence representation profile that is substantially the same as said initial sequence representation profile, as recited by the pending claims. Furthermore, it was well within the skill of the ordinarily skilled artisan to acquire such sets of nucleic acids, for example by performing RT-PCR on cells of interest and preparing a bacterial library of the cDNAs; or by preparing select nucleic acids individually, e.g. to form a collection of nucleic acids representative of a gene family; or by purchasing one of many commercially available nucleic acid collections, e.g. ESTs from IMAGE or Riken. Thus, one of ordinary skill in the art would predict that non-cellular nucleic acid libraries representative of other sets of separate nucleic acids could, in fact, be generated from any initial set of separate nucleic acids.

In response, the Examiner asserts on page 17, lines 4-7, that:

Absent any showing to the contrary and indication that the single species would be representative for the huge scope of any EST using the broad process steps, the genus claim is not adequately described."

The Examiner, quoting from *In re Curtis*, asserts on page 18, lines 1-6, that:

Applicant, at the time of filing, is deemed to have not invented species sufficient to constitute the genus by virtue of having disclosed a single species when . . . the evidence indicates [that] ordinary artisans could not predict the operability in the invention of any species other than the one disclose. (emphasis added)

Applicants submit that the Examiner has provided no evidence to suggest that the invention could not work for any species other than the one disclosed. Furthermore, Applicants submit that the art actually provides a plethora of examples *supporting* the notion that the method of the pending claims could be used to produce non-cellular nucleic acid libraries from any nucleic acid starting material regardless of the type of cell/tissue that was the source material or the organism from which the source material was derived. For example:

- **Gubler et al.** ((1983) *Gene* 25:263-269) (Exhibit A) teaches a method for generating nucleic acid libraries from submicrogram quantities of mRNA (abstract). Gubler et al. teaches using rabbit reticulocyte RNA (p. 265, col. 1, last paragraph), bovine adrenal medulla RNA (p. 267, col. 1, last paragraph), and other sources to generate "about half a dozen libraries from different mRNA sources." (p. 269, col. 1, first full paragraph). Lawton et al. ((1988) *Plant Physiol.* 90:690-696) (Exhibit B) uses the method to generate a library from RNA from carnation petals. Mohapatra et al. ((1989) *Plant Physiol.* 89:375-378) (Exhibit C) uses the method to generate libraries from alfalfa seedlings. Stewart et al. ((1993) *J. Exp Med.* 177:409-418) (Exhibit D) uses the method to generate libraries from the peripheral blood mononuclear cells (PBMCs) of two individuals, a Caucasian and an Asian.
- **Zhu et al.** ((2001) *Biotechniques* 30(4):892-7, abstract) (Exhibit E) teaches a method for generating nucleic acid libraries that relies on SMART technology, a technology that exploits the template-switching activity of Moloney murine leukemia virus reverse transcriptase to both synthesize and anchor first-strand

cDNA in one step. Zhu et al. uses the method to generate a nucleic acid library from human skeletal muscle RNA. Yao et al. ((2004) *Physiol Genomics* 19(1):84-92, abstract) (Exhibit F) uses the method to generate a nucleic acid library from bovine oocytes. Wellenreuther et al. ((2004) *BMC Genomics* 5(1):36) (Exhibit G) uses the method to generate a nucleic acid library from an endometrium carcinoma cell line. Liu et al. ((2002) *Sheng Wu Gong Cheng Xue Bao* 18(6):749-53, abstract) (Exhibit H) uses the method to generate a nucleic acid library from the tentacles of *Sagartia rosea*. Zhang et al. ((2003) *DNA Seq.* 14(6):413-9, abstract) (Exhibit I) uses the method to generate a nucleic acid library from *Campoletis chloridae*. Clontech markets a kit (the "SMART cDNA Library Construction Kit", Exhibit J) that relies on the method of Zhu et al. to generate "cDNA libraries from nanogram amounts of total or polyA⁺ RNA" (Description). Clontech is silent with regard to restrictions on the source of nucleic acid material.

- **Ohara et al.** ((2001) *Nucleic Acids Research* 29(4), p.1-8) (Exhibit K) teaches a method of making a nucleic acid library that relies on an in vitro site-specific recombination reaction for cloning the nucleic acids. Ohara et al. uses the method to generate a nucleic acid library from rat brain poly(A⁺) RNA, and teaches "To date, we have successfully constructed several different cDNA libraries by this method" (p. 7, col. 2, 3d paragraph). Ohara et al. ((2002) *DNA Research* 9:47-57) (Exhibit L) uses the method to generate cDNA libraries from adult mouse brain, embryonic mouse intestinal tract, adult mouse thymus, embryonic mouse tail, and human brain tissues. Invitrogen markets a kit (the "SuperScript Full Length cDNA Library Construction Kit", Exhibit M) that relies on the method of Ohara et al. to generate cDNA libraries. Invitrogen is silent with regard to any restrictions on the source of nucleic acid material.
- **Golemis et al.** ((1999) *Curr. Prot. Mol. Biol.* 20.1.1-20.1.40) (Exhibit N) teaches a method of making a nucleic acid library for use in yeast two hybrid screening. Golemis et al. teaches libraries that have been made using this method include libraries made from cell lines, cancer cell lines, human tissue, mouse tissue, rat tissue, *D. melanogaster* tissue, yeast, sea urchin ovary, *C. elegans*, *Agrobacterium*, *Arabidopsis*, tomato and *Xenopus laevis*, where those tissues

include breast, liver, lung, brain, testis, ovary, placenta, heart, mammary gland, peripheral blood leukocytes, kidney, spleen, prostate, fetal prostate, fetal liver, fetal brain, and so on; see Table 20.1.3 on pages 20.1.14-16 for more details.

- **Clontech** markets a kit (the "Make Your Own 'Make & Plate' Library" kit) (Exhibit O) for making a nucleic acid library for use in yeast two hybrid screening, which relies upon SMART technology and an in vitro site-specific recombination reaction for cloning the nucleic acids. Clontech is silent with regard to any restrictions on source material. Furthermore, in related material ("Mate & Plate™ Yeast Two-Hybrid cDNA Libraries", Exhibit P), Clontech teaches 12 commercially available libraries made from human tissue and mouse tissue, and from bone marrow, fetal brain, heart, liver, skeletal muscle, testis, ovary, and embryo, using their kit (see table, p. 2).

Thus, the art provides a wealth of evidence demonstrating that methods for making nucleic acid libraries can be used with any source of the nucleic acid material and that, contrary to the Examiner's assertions, the ordinarily artisan would, in fact, predict that the operability in the invention would extend to any nucleic acid species in view of the one disclosed. Accordingly, Applicants submit that in view of the art, the specification does indeed describe the nucleic acid library that is produced by the pending claimed method in sufficient detail that the one of ordinary skill in the art would reasonably conclude that the inventor had possession of the claimed invention.

Reconsideration and withdrawal of the rejection is respectfully requested.

REJECTIONS UNDER §112, ¶2

Claims 27-34 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner asserts that Claim 27 is indefinite for use of the phrase "two or more" in step (b) of the claim. Applicants have amended the claim to remove this phrase. In view of this amendment, this rejection may be withdrawn.

REJECTIONS UNDER §102

I. Claims 27-34 are rejected under 35 U.S.C. 102(e) as allegedly anticipated by Edwards et al. (US 7,235,381).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, (Fed. Cir. 1987).

The standard for anticipation under section 102 is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). Further, an anticipatory reference must be enabling, see *Akzo N.V. v. United States Int'l Trade Comm'n* 808 F.2d 1471, 1479, 1 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986), *cert denied*, 482 U.S. 909 (1987), so as to place one of ordinary skill in possession of the claimed invention. To anticipate a claim, a prior art reference must disclose every feature of the claimed invention, either explicitly or inherently. *Glaxo v. Novopharm, Ltd.* 334 U.S. P.Q.2d 1565 (Fed. Cir. 1995).

Claim 27, from which the remaining pending claims depend, recites a method of producing a non-cellular nucleic acid library, the method comprising: “(a) dividing an initial set of a plurality of separate nucleic acids into at least two pooled collections of nucleic acids having an initial sequence representation profile, wherein each pooled collection includes not more than about 100 distinct nucleic acids; (b) amplifying each of said pooled collections to produce amplified pooled collections; and (c) combining said amplified pooled collections to produce said non-cellular nucleic acid library, wherein said non-cellular nucleic acid library is a collection of separate nucleic acids with a sequence representation profile that is substantially the same as said initial sequence representation profile.” Thus, the methods call for pooling distinct nucleic acids, amplifying the pools, and pooling those amplified pools.

Applicants maintain that Edwards et al. does not anticipate the pending claims because Edwards et al. does not disclose amplifying pooled collections of nucleic acids to produce two or more pooled collections, or pooling these pools. Edwards et al. teaches making RNA from various tissues (Example 1) or from 5' ESTs from cDNA or genomic libraries (Example 7), synthesizing cDNA from that RNA (Example 2) and cloning that cDNA (Example 3). Edwards teaches fractionating that cDNA by size and pooling the cDNAs greater than 150bp (Example

4); selecting those cDNAs with a 5' oligo tag (Example 5) and transforming them into bacteria. However, nowhere in Edwards et al.'s procedure does Edwards et al. disclose amplifying pooled collections of initial sets of nucleic acids, or pooling amplified products; for example, Edwards et al. does not amplify the pools of cDNAs greater than 150bp. Edwards et al. is silent on amplification of pooled collections of nucleic acids. Because Edwards et al. does not disclose every step of the pending claimed method, Edwards et al. cannot anticipate the pending claims.

In response, the Examiner states that "attention is drawn to Edwards' reference at e.g. col. 59, which recites that the multiple copies result from amplification of a chromosomal sequence." (Final Office Action, p. 22, l. 10-12).

Applicants respectfully submit that they can find no mention of amplification in col. 59 of by Edwards et al. (US 7,235,381). Furthermore, the only mention of multiple copies resulting from amplification of chromosomal sequence that Applicants can find, at col. 107, l. 9-15, is unrelated to the amplification of pooled collections recited by the pending claims. In this passage, Edwards et al. teaches:

The secretion vector may be DNA or RNA and may integrate into the chromosome of the host, be stably maintained as an extrachromosomal replicon in the host, be an artificial chromosome, or be transiently present in the host. Preferably, the secretion vector is maintained in multiple copies in each host cell. As used herein, multiple copies means at least 2, 5, 10, 20, 25, 50 or more than 50 copies per cell. In some embodiments, the multiple copies are maintained extrachromosomally. In other embodiments, the multiple copies result from amplification of a chromosomal sequence.

Applicants respectfully submit that this teaching addresses the maintenance and expression of a cloned cDNA in a cell. In the passages prior to this one, Edwards teaches that, secretion vectors can be constructed that are capable of directing the secretion of the proteins encoded therein (col. 106, l. 43-55). In the passage at col. 107, cited above, Edwards teaches that it is preferable that multiple copies of a secretion vector be maintained inside the cell, and teaches that this can be achieved amplification of a chromosomal sequence. However, relevant to the pending claims this "amplification of a chromosomal sequence" is not an amplification of a pooled collection of nucleic acids; rather, it is amplification of the single secretion vector that has integrated into a chromosome. Furthermore, Edwards does not disclose pooling this amplified sequence with any other. Thus, Applicants maintain that Edwards et al. does not

disclose amplifying pooled collections of initial sets of nucleic acids, or pooling amplified products, as recited in the pending claims.

In view of these remarks, reconsideration and withdrawal of the rejection is requested.

II. Claims 27, 30, 32, 33 and 34 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Chengtao et al. (Chinese Journal of Biochemistry, 1999.)

As discussed above, Claim 27, from which the remaining pending claims depend, recites a method of producing a non-cellular nucleic acid library, the method comprising: "(a) dividing an initial set of a plurality of separate nucleic acids into at least two pooled collections of nucleic acids having an initial sequence representation profile, wherein each pooled collection includes not more than about 100 distinct nucleic acids; (b) amplifying each of said pooled collections to produce amplified pooled collections; and (c) combining said amplified pooled collections to produce said non-cellular nucleic acid library, wherein said non-cellular nucleic acid library is a collection of separate nucleic acids with a sequence representation profile that is substantially the same as said initial sequence representation profile." Thus, the methods call for pooling distinct nucleic acids, amplifying the pools, and pooling those amplified pools.

Applicants maintain that Chengtao et al. does not anticipate the pending claims because Chengtao et al. does not disclose any steps of the pending claimed method. Chengtao et al. teaches annealing synthetic single strand DNA to make double strand fragments 2, 6, or 8, filling in the ends and cutting with enzymes, and ligating into vector VR1012 to form monoclonal of 2, 6, or 8 (2.1.1). Chengtao et al. teaches cutting out these DNA fragments from the monoclonal with enzymes, and recloning the three different fragments into 1 vector (2.1.2). However, nowhere in Chengtao et al.'s procedure does Chengtao et al. disclose pooling initial sets of distinct nucleic acids, amplifying the pooled collections, and pooling amplified products; for example, Chengtao et al does not pool the DNA fragments cut from the monoclonal, or amplify those fragments, or pool those amplified products. Chengtao et al. is silent on pooling and amplification.

Because Chengtao et al. does not disclose every step of the pending claimed method, Chengtao et al. cannot anticipate the pending claims. At the conclusion of the telephone interview on July 8, 2010, the Examiner agreed that the claims patentably distinguished over the

cited reference by Chengtao and that this rejection would be withdrawn upon filing of this response.

Thus, withdrawal of the rejection is requested.

III. Claims 27-28, 30 and 32 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Okazaki et al. (Nature, 2002).

As discussed above, Claim 27, from which the remaining pending claims depend, recites a method of producing a non-cellular nucleic acid library, the method comprising: "(a) dividing an initial set of a plurality of separate nucleic acids into at least two pooled collections of nucleic acids having an initial sequence representation profile, wherein each pooled collection includes not more than about 100 distinct nucleic acids; (b) amplifying each of said pooled collections to produce amplified pooled collections; and (c) combining said amplified pooled collections to produce said non-cellular nucleic acid library, wherein said non-cellular nucleic acid library is a collection of separate nucleic acids with a sequence representation profile that is substantially the same as said initial sequence representation profile." Thus, the methods call for pooling distinct nucleic acids, amplifying the pools, and pooling those amplified pools.

Applicants maintain that Okazaki et al. does not anticipate the pending claims because Okazaki et al. does not disclose amplifying pools of nucleic acids or pooling amplified pooled collections. Okazaki et al. teaches dividing an initial set of cDNAs into 171,144 clusters based on sequence similarity (paragraph bridging p. 563 and 564), and sequencing cDNAs representative of those clusters. However, nowhere in Okazaki et al's procedure does Okazaki et al. disclose amplifying pooled collections of initial sets of nucleic acids, or pooling those amplified products. Okazaki et al. is silent on amplification of pooled collections of nucleic acids. Because Okazaki et al. does not disclose every step of the pending claimed method, Okazaki et al. cannot anticipate the pending claims.

In response, the Examiner states that "attention is drawn to the disclosure of Okazaki et al. which teaches that sets were paired and amplified. Furthermore, it is unclear as to how Okazaki could produce the genomic region if it is not amplified". (p. 26, l. 8-11) In the telephonic interview, the Examiner points to the paragraph bridging pages 563 and 564 and the

Supplementary Information to which this passage refers for providing this disclosure.

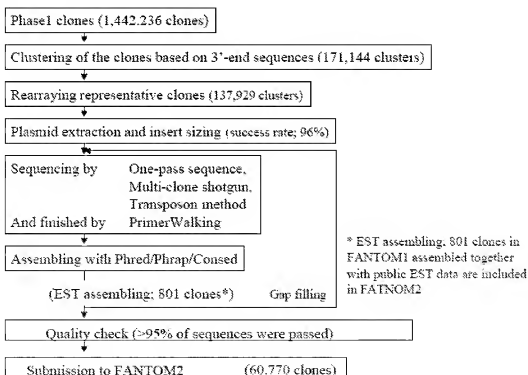
The paragraph bridging pages 563-564 and the Supplementary Information to which it refers is reproduced below:

The FANTOM2 clone set

The cDNA clones used in the project were selected from 246 full-length enriched cDNA libraries, most of which were also normalized and subtracted, with most from C57BL/6 mice, as described elsewhere^{12,14,15}. Information about tissue source and other information regarding these libraries is available in Supplementary Information section 1.

1,442,236 sequences were grouped into 171,144 3'-end clusters based on sequence similarity (Supplementary Information section 2)¹⁴⁻¹⁶. Of these, 159,789 had no significant BLAST hit to known mouse genes, and were considered potentially novel. However, from the annotation of the FANTOM1 clone set¹² it became clear that alternative polyadenylation is common in the mouse transcriptome, and that the set of 3'-end clusters is significantly redundant. To address this problem, 547,149 of these clones were sequenced from their 5' ends to provide additional discrimination.

Supplementary Information 2



Applicants respectfully submit that they can find no disclosure in the cited passages of amplifying pooled nucleic acids. The nucleic acids aren't even pooled in Okazaki et al; rather, the clustering occurs virtually, i.e. on a computer, based upon the 3'-end sequences of the individual cDNAs. After clustering and analysis by computer, the scientists in Okazaki et al. return to the original cDNA clones and sequence 547,149 of them from the 5' ends to provide additional sequence discrimination. Thus, Applicants maintain that Okazaki et al. is silent on amplification of pooled collections of nucleic acids, and pooling those amplified pooled collections.

Because Okazaki et al. does not disclose every step of the pending claimed method, Okazaki et al. cannot anticipate the pending claims. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-285.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: September 14, 2010

By: /Elizabeth A. Alcamo, Ph.D, Reg. No. 64,133/

Elizabeth A. Alcamo, Ph.D.
Registration No. 64,133

Date: September 14, 2010

By: /Bret E. Field, Reg. No. 37,620/

Bret E. Field
Registration No. 37,620

Exhibits:

- Exhibit A. Gubler et al. ((1983) Gene 25:263-269)
- Exhibit B. Lawton et al. ((1988) Plant Physiol. 90:690-696)
- Exhibit C. Mohapatra et al. ((1989) Plant Physiol. 89:375-378)
- Exhibit D. Stewart et al. ((1993) J. Exp Med. 177:409-418)
- Exhibit E. Zhu et al. ((2001) Biotechniques 30(4):892-7) (abstract)
- Exhibit F. Yao et al. ((2004) Physiol Genomics 19(1):84-92) (abstract)
- Exhibit G. Wellenreuther et al. ((2004) BMC Genomics 5(1):36)
- Exhibit H. Liu et al. ((2002) Sheng Wu Gong Cheng Xue Bao 18(6):749-53) (abstract)
- Exhibit I. Zhang et al. ((2003) DNA Seq. 14(6):413-9) (abstract)
- Exhibit J. Clontech "SMARTTM cDNA Library Construction Kit" manual
- Exhibit K. Ohara et al. ((2001) Nucleic Acids Research 29(4), pp.1-8)
- Exhibit L. Ohara et al. ((2002) DNA Research 9:47-57)
- Exhibit M. Invitrogen "SuperScriptTM Full Length cDNA Library Construction Kit" manual
- Exhibit N. Golemis et al. ((1999) Curr. Prot. Mol. Biol 20.1.1-20.1.40)
- Exhibit O. Clontech "Make Your Own 'Make & Plate'TM Library Kit" manual
- Exhibit P. Clontech "Mate & PlateTM Yeast Two-Hybrid cDNA Libraries" literature

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231